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(54) Title: COMPOSITIONS OF CLINDAMYCIN AND BENZOYL PEROXIDE FOR ACNE TREATMENT

(57) Abstract

Compositions suitable for the treatment of acne by topical application comprise clindamycin and benzoyl peroxide. Kits for preparing the compositions include a solution of clindamycin in a first container and a gel suspension of benzoyl peroxide in a second container. Each component is stored at a pH which promotes stability, and the combination of the two components provides a final composition having a pH which promotes stability and enhances viscosity.

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COMPOSITIONS OF CLINDAMYCIN AND BENZOYL PEROXIDE FOR ACNE TREATMENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to compositions and methods for formulating compositions for treatment of acne. More particularly, the present invention relates to compositions comprising benzoyl peroxide and clindamycin for treatment of acne by topical administration.

Acne is a common skin disorder characterized by blackheads, whiteheads, papules, pustules, cysts, and various sized nodules and scars which, in the inflammatory state of the disorder, are contaminated with bacteria such as *Propionibacterium acnes*. The disorder effects skin areas where the sebaceous glands are most active, and bacterial infection can occur in the sebaceous follicles.

A variety of acne treatment methods have been developed, including both systemic and topical administration of antibiotics, topical administration of organic peroxides, particularly benzoyl peroxide, and the like. Of particular interest to the present invention is the topical administration of antibiotic compositions and other active ingredients, such as benzoyl peroxide.

A particularly effective topical composition for the treatment of acne is a combination of erythromycin, a topical antibiotic, and benzoyl peroxide, as described in U.S. Patent No. 4,497,794. Compositions prepared generally as described in the '794 patent are sold under the tradename Benzamycin® by Dermik Laboratories, Inc., Collegeville, Pennsylvania. Benzamycin® is widely prescribed for the treatment of acne and is recognized in some cases to be more effective than treatment with either erythromycin or benzoyl peroxide alone.

The use of products which combine erythromycin and benzoyl peroxide, however, suffers from certain disadvantages. The combination of erythromycin and benzoyl peroxide is unstable and requires refrigeration for storage. The need to refrigerate the product is not only inconvenient for the patient (e.g., it is difficult to continuously refrigerate the

product when travelling), the application of a cold medicine to the face is often unpleasant and reduces patient compliance. The need to store the product in a refrigerator can further reduce patient compliance since the product is "hidden away."

The Benzamycin® product suffers from particular formulation problems. In order to prepare the product, a pharmacist must dissolve erythromycin powder in alcohol from the pharmacy stock. Variations in particular alcohols which are available can lead to variability in the compounded product. Moreover, improper compounding by the pharamacist is possible because of the variable dissolution of erythromycin in alcohol resulting in partially dissolved or undissolved aggregates of the drug. As a result, the effective dosage of the compounded product can vary, and some patients have reported that the product sometimes feels "gritty" when applied to the skin.

For these reasons, it would be desirable to provide improved compositions and methods for formulating compositions for the treatment of acne. In particular, it would be desirable to provide products which combine the activity of an antibiotic compound with the activity of benzoyl peroxide, with none or fewer of the disadvantages described above for the combination of erythromycin and benzoyl peroxide. Such compositions should be effective in treating acne, preferably being at least as effective as the use of erythromycin/benzoyl peroxide compositions and more preferably being more effective than erythromycin/benzoyl peroxide compositions. The compositions should also overcome the formulation and stability problems which have been associated with the erythromycin/benzoyl peroxide compositions. That is, the improved compositions should be easy to formulate, should have a smooth consistency after formulation, should be adequately stable, and should have a sufficiently long storage life even without refrigeration.

2. <u>Description of the Background Art</u>

U.S. Patent No. 4,497,794, discloses compositions combining erythromycin and benzoyl peroxide for the treatment of acne, as described above. Other patents disclosing the

combination of erythromycin and benzoyl peroxide for acne treatment and other purposes include U.S. Patent No. 4,411,893; U.S. Patent No. 4,692,329; and British Patent No. 1,594,314. The combination of erythromycin with other organic peroxides for the treatment of acne is described in British Patent No. 2,088,717. Other formulations containing benzoyl peroxide for the treatment of acne are described in U.S. Patent Nos. 3,535,422; 4,056,611; 4,318,907; 4,923,900; 4,387,107; and 4,228,163. Other peroxide formulations for treating acne are described in U.S. Patent No. 4,607,101. The use of clindamycin and other lincomycin antibiotics for the treatment of acne is described in U.S. Patent No. 3,969,516. Hirschmann (1988) Arch. Dermatol. 124:1691-1700 and Fulton, Jr., et al. (1974) Arch. Dermatol. 110:83-86 describe the topical use of antibiotics for the treatment of acne.

SUMMARY OF THE INVENTION

The present invention provides novel acne treatment compositions comprising both clindamycin, an antibiotic effective against *Propionibacterium acnes,* and benzoyl peroxide, a keratolytic and desquamative agent which further possesses a broad antibacterial activity. The two agents are combined in a pharmaceutically acceptable fluid carrier, usually a gel, which has been found to provide effective topical treatment of acne. The benzoyl peroxide will be present in the carrier at a concentration from 1% by weight to 20% by weight and the clindamycin will be present at a concentration from 0.2% by weight to 4% by weight. By maintaining the compositions at a pH below 7, the tendency of benzoyl peroxide to oxidize and degrade clindamycin is largely overcome and the product remains stable during storage at room temperature for extended periods, typically several months or longer. Additionally, the compositions of the present invention have been found to remain substantially odor free even after storage at room temperature for extended periods. This is surprising since clindamycin solutions frequently develop a strong offensive odor upon aging. The presence of such an odor is unacceptable in topical formulations which are to be applied to a patient's face.

In a particular aspect of the present invention, the topical compositions are prepared by combining or admixing an aqueous gel suspension of benzoyl peroxide with an aqueous solution of a clindamycin salt or ester. Prior to combination, the two components are maintained individually, each at a pH selected to enhance stability of the component by itself. The individual pH of each component is further selected so that, after combination, the pH of the final admixed product will produce a pH below 7 to provide stability at room temperature during a normal period of use, as described above. More specifically, the pH of the aqueous clindamycin solution is adjusted to a pH in the range from 3.5 to 7, where it is stable and can remain in solution for extended periods. The aqueous suspension of benzoyl peroxide is stored at a pH from 3.5 to 7.0, typically with a gelling agent which has a relatively low viscosity at the storage pH. By combining preselected amounts of the two components, the pH of the combination will be below 7 and the combination will remain stable for several months after admixture at room temperature.

Preparation of the topical compositions by combining two separately maintained components has a number of advantages. While the topical composition itself is stable for a period of months at room temperature, the individual components will be stable for much longer periods, typically for at least two years or longer. Thus, the components may be prepackaged and will have an acceptable shelf life after distribution. The individual components of the present invention are easily formulated prior to use. The benzoyl peroxide is present as a stable suspension and the clindamycin is present as a stable solution, and their combination requires simple mixing without the need to dissolve any dry components. Moreover, there is no need to combine any other ingredients, such as alcohol, from the pharmacist's stock solutions, thus lessening product variability. Additionally, by properly selecting the gelling agent, the initial viscosity of the benzoyl peroxide suspension (at the suspension pH) may be relatively low, while the viscosity of the final product (at the product pH), can be relatively high to provide a desired

gel consistency. Thus, the components may be easily combined by a pharmacist to provide a gel having a pleasing consistency and texture for use by the patient.

The present invention further provides a kit for preparation of the topical composition from the individual components. The kit will comprise a first container holding the benzoyl peroxide suspension and a second container holding the aqueous solution of clindamycin salt or ester. In addition, the kit will include instructions to combine the benzoyl peroxide suspension with the clindamycin solution to provide the topical composition. Optionally, the kit may include a disposable mixing spatula for the convenience of the dispensing pharmacist.

The present invention still further comprises methods for treating acne by applying the topical composition to affected areas of the patient's skin.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a kit according to the present invention.

Fig. 2 illustrates the loss of clindamycin in an experimental formulation according to the present invention after admixture of the components and accelerated aging for one month at 40°C.

DESCRIPTION OF THE PREFERRED EMBODIMENT

According to the present invention, topical compositions for the treatment of acne include both clindamycin and benzoyl peroxide present in a fluid carrier or vehicle which is formulated to enhance stability, efficacy, and aesthetic acceptability of the compositions. The clindamycin constituent will be a pharmaceutical grade salt or ester, usually being clindamycin phosphate. Clindamycin phosphate (ester) is preferred over clindamycin hydrochloride (salt) because of its wider compatibility with gelling agents and its more extensive history of topical use. The preparation of suitable clindamycin and equivalent lincomycin compounds are described in U.S. Patent No. 3,969,516, the disclosure of which is incorporated herein by reference. Pharmaceutical grade clindamycin phosphate is available from commercial suppliers,

such as Genzyme Corporation, One Kendall Square, Cambridge, Massachusetts 02139.

The benzoyl peroxide constituent will be pharmaceutical grade. It may be in the form of a slurry of a finely divided powder, typically having a mean particle size of 35 μm, or lower, or in the form of a hydrous granular material which will have its particle size reduced accordingly during processing according to this invention. Preparation of suitable benzoyl peroxide constituents is well described in the medical and patent literature. See, for example, the U.S. Patent Nos. 3,535,422; 4,056,611; 4,387,107; and 4,923,900, the disclosures of which are incorporated herein by reference. Suitable benzoyl peroxide raw materials are available from commercial suppliers, such as the Norac Company, Azusa, California.

The clindamycin and benzoyl peroxide constituents will be combined in a suitable fluid vehicle or carrier, typically an aqueous carrier, and will preferably be further combined with an aqueous gelling agent, such as neutral, anionic, and cationic polymers, and mixtures thereof. Exemplary polymers include carboxy vinyl polymers, preferably carboxypolymethylene (CAS Registry No. 9007-209) which is commercially available under the tradename Carbopol®, from B.F. Goodrich Chemical Company, Cleveland, Ohio 44138. The most preferred gelling agent is Carbopol®. Other suitable gelling agents include cellulosic polymers, such as gum arabic, gum tragacanth, locust bean gum, guar gum, xanthan gum, cellulose gum, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

As discussed in more detail below, the gelling agent will usually be initially combined with an aqueous suspension of benzoyl peroxide to form a first component of a two component kit for formulating the topical composition. The gelling agent ideally will be selected to have a reduced viscosity at the pH of the first component and an increased viscosity at the stage of the final product obtained when the two components are combined.

Other ingredients which may optionally be provided in the topical compositions include humectants, such as propylene glycol; solvents, such as alcohol; and anti-microbial preservatives, such as methylparaben and propylparaben. The topical compositions will also include an organic or inorganic base, such as potassium hydroxide, which is used to adjust the pH of the initial components and the final product, as described in more detail hereinbelow.

Table 1 sets forth exemplary formulations for the topical compositions of the present invention and Table 2 sets forth a preferred formulation.

TABLE 1

Constituent	Weight Percent[1] Broad Range	Preferred Range
Clindamycin	0.2% to 4%	1% to 2%
Benzoyl peroxide	1% to 20%	2.5% to 10%
Gelling agent	0.1% to 5%	0.5% to 2%
Humectant	0% to 30%	5% to 15%
Antimicrobial preservative	0% to 2%	0.1% to 0.5%
Solvent	0% to 50%	0% to 20%
Buffer, acid or base	pH4 to <pH7	pH4.5 to pH5.5

[1] Based on total weight in purified water or other suitable fluid carrier.

TABLE 2

Constituent	Weight Percent[1]
Clindamycin	1.0
Benzoyl peroxide	5.0
Carboxyl vinyl polymer	1.25
Propylene glycol	10.0
Methylparaben	0.2
Propylparaben	0.05
pH	5.0

[1] Based on total weight in purified water.

The two-component kit will comprise an aqueous solution of clindamycin having a concentration in the range from 2% to 15% by weight, preferably being in the range from 8% to 12% by weight. It is important that the pH of the solution be maintained within a range from 3.5 to 7, preferably within a range from 6 to 6.5, in order to inhibit precipitation of the clindamycin from the solution, particularly when the solution

is exposed to cold temperatures during storage. The pH of an aqueous clindamycin phosphate solution is normally about 3.5, and the pH of the clindamycin component may be increased to within the desired range by the addition of a pharmaceutically acceptable buffer or base, such as potassium hydroxide.

The benzoyl peroxide component of the two-component kit will comprise an aqueous suspension (stable dispersion) of benzoyl peroxide and a concentration in the range from 1% to 20% by weight, preferably in the range from 5% to 10% by weight. The benzoyl peroxide component will also contain the gelling agent, when a gelling agent is present in the combined topical composition. By properly selecting the nature of the gelling agent and the pH of the benzoyl peroxide component, the benzoyl peroxide component itself may be maintained at a relatively low viscosity while the final topical composition (which is at a different pH) will have a relatively higher viscosity. In this way, mixing of the two components to form the topical composition is facilitated (i.e. the lower viscosity of the benzoyl peroxide component makes the combination and mixing with the clindamycin component easier) while the final topical composition can still possess the desired higher viscosity, gel consistency.

Preferably, the viscosity of the benzoyl peroxide component will be below about $9x10^4$ cp, usually being in the range from $5x10^4$ cp to $9x10^4$ cp, more preferably being in the range from $6.5x10^4$ cp to $8.5x10^4$ cp, while the viscosity of the final topical composition product will be in the range from $7x10^4$ cp to $12x10^4$ cp, more preferably being in the range from $8x10^4$ cp to $10x10^4$ cp. These viscosities may be achieved using the polymeric gelling agents, as described above, and a benzoyl peroxide component having a pH in the range from 3.5 to 7.0, preferably in the range from 4.0 to 5.0. The pH may be adjusted by the addition of a pharmaceutically acceptable buffer or base, such as potassium hydroxide. When the benzoyl peroxide component is combined with the clindamycin component, the resulting combined product will have an increased pH resulting in enhanced viscosity within the range set forth above.

is exposed to cold temperatures during storage. The pH of an aqueous clindamycin phosphate solution is normally about 3.5, and the pH of the clindamycin component may be increased to within the desired range by the addition of a pharmaceutically acceptable buffer or base, such as potassium hydroxide.

The benzoyl peroxide component of the two-component kit will comprise an aqueous suspension (stable dispersion) of benzoyl peroxide and a concentration in the range from 1% to 20% by weight, preferably in the range from 5% to 10% by weight. The benzoyl peroxide component will also contain the gelling agent, when a gelling agent is present in the combined topical composition. By properly selecting the nature of the gelling agent and the pH of the benzoyl peroxide component, the benzoyl peroxide component itself may be maintained at a relatively low viscosity while the final topical composition (which is at a different pH) will have a relatively higher viscosity. In this way, mixing of the two components to form the topical composition is facilitated (i.e. the lower viscosity of the benzoyl peroxide component makes the combination and mixing with the clindamycin component easier) while the final topical composition can still possess the desired higher viscosity, gel consistency.

Preferably, the viscosity of the benzoyl peroxide component will be below about $9x10^4$ cp, usually being in the range from $5x10^4$ cp to $9x10^4$ cp, more preferably being in the range from $6.5x10^4$ cp to $8.5x10^4$ cp, while the viscosity of the final topical composition product will be in the range from $7x10^4$ cp to $12x10^4$ cp, more preferably being in the range from $8x10^4$ cp to $10x10^4$ cp. These viscosities may be achieved using the polymeric gelling agents, as described above, and a benzoyl peroxide component having a pH in the range from 3.5 to 7.0, preferably in the range from 4.0 to 5.0. The pH may be adjusted by the addition of a pharmaceutically acceptable buffer or base, such as potassium hydroxide. When the benzoyl peroxide component is combined with the clindamycin component, the resulting combined product will have an increased pH resulting in enhanced viscosity within the range set forth above.

The variation of viscosity with pH in a preferred Carbopol® gelling agent is as set forth in Table 3:

TABLE 3

Effect of pH on Viscosity of 0.5 Weight % Solutions of Carbopol® 940

pH	CP
4.0	23,500
4.5	38,500
5.0	48,500
6.0	56,800
6.5	57,800
7.0	57,900

Thus, it can be seen that a beneficial increase in viscosity can be achieved by increasing the pH of the final (combined) product relative to the initial pH of the benzoyl peroxide component containing the gelling agent.

The additional constituents, such as the anti-microbial agents, solvents, humectants, and the like, may be present in either the clindamycin component, the benzoyl peroxide component, or both. Such constituents will be present in the individual kit components at concentrations which results in the desired final concentrations in the topical composition, such as set forth in Table 1 above.

The clindamycin component and the benzoyl peroxide component will be stored in separate, sealed containers, such as bottles, jars, vials, ampules, tubes, pouches, and the like, with the two containers usually being packaged together in the form of a kit, usually including instructions on how to admix the final product, and optionally including a mixing spatula. In this way, the kits may be manufactured, distributed, and stored at remote locations where they will be used, typically pharmacies, hospitals, doctor's offices, and the like. The kits will have an extended shelf life, typically being at least a year, usually being at least two years, or longer so long as the clindamycin component and benzoyl peroxide component are formulated as described above.

Conveniently, when packaged together as a kit 10 (Fig. 1), the benzoyl peroxide component will be stored as a

low viscosity gel in a jar or other container suitable for mixing. The kit instructions (not illustrated) will call for combining the contents of the clindamycin component container, typically a vial 14, into the benzoyl peroxide container 12 and for subsequently mixing the combination to a uniform consistency. Optionally, the kit 10 may include a disposable spatula 16 for mixing so that the user or pharmacist need not employ any outside materials to formulate the final topical composition.

The relative amounts of the benzoyl peroxide composition and the clindamycin composition in each of the containers will be selected to provide the desired final volume of the topical composition as well as providing the desired final concentrations of the active constituents. Preferably, the ratio of clindamycin solution component to benzoyl peroxide suspension component is in the range of 1 or 2 to 9. Larger proportions of the clindamycin solution can be used, for example, a 1 to 1 ratio of the components, however such a ratio is less preferred because of the increased mixing time required to achieve homogeneity of the admixture. For example, the mixing time for a 1 to 1 ratio of components is twice as long or longer than that for the preferred ratio of about 1 or 2 to 9. The ability to maintain the preferred ratio is at least partly the result of stable incorporation of relatively high concentrations of clindamycin in the clindamycin component at the preferred pH range from 6 to 6.5.

Usually, the total weight of topical composition prepared from a single kit will be in the range from 5g to 120g, usually being in the range from 15g to 45g. When the clindamycin component is to be added to the benzoyl peroxide component, the weight of the benzoyl peroxide will typically be greater, usually being in the range from 2.5g to 100g, more usually being in the range from 12g to 40g. The weight of the clindamycin component will usually be in the range from 0.5g to 60g, more usually being in the range from 1.5g to 7g. The precise weights, volumes, constituent concentrations, pH levels, and the like, are of course all interdependent and must be finally selected to provide the desired characteristics set

forth above for the final and mixed product. The determination of the precise formulations for the individual constituents is well within the skill of the art.

The fully formulated (admixed) topical compositions of the present invention may be stored at room temperature and will remain stable, i.e. without substantial loss of efficacy or unacceptable loss of the clindamycin content, for extended periods, typically for at least one month, frequently for two months or longer, and usually for three months or longer.

The topical compositions of the present invention are used to treat acne by applying a thin layer of the composition to the affected area of the skin. Usually, from 0.1g to 1g of the topical composition will be applied in a single application, with applications being repeated at least daily, usually being repeated twice daily, and sometimes being repeated at frequency of three times daily or greater.

The following examples are offered by way of illustration, not by way of limitation.

EXPERIMENTAL

Examples 1-4

Aqueous solutions of clindamycin (Genzyme Corp.) were prepared as follows:

	Weight Percent			
Component	Ex. 1	Ex. 2	Ex. 3	Ex. 4
Clindamycin Phosphate Ester	10.58	2.38	14.28	0
Clindamycin Hydrochloride Salt	0	0	0	7.50
Methylparaben	0.10	0.10	0	0.10
Propylparaben	0.02	0.02	0	0.02
Imidurea	0	0	0.3	0
Potassium Hydroxide, 10% Aqueous Solution (QS)	pH 6.2	pH 4.5	pH 6.5	pH 6.9
Purified Water (QS ad)	100.00	100.00	100.00	100.00

The methylparaben and propylparaben or imidurea were first dissolved in water equivalent to about 75% of the total batch amount. Next, the clindamycin component was added and mixed. After the clindamycin had mostly dissolved, the potassium hydroxide solution was added incrementally (while mixing) to reach the desired pH. Finally, water was added to make the formulation total 100%.

Examples 5-8

Benzoyl peroxide aqueous suspensions were prepared as follows:

Component	Weight Percent Ex. 5	Ex. 6	Ex. 7	Ex. 8
Hydrous Benzoyl Peroxide, USP (70%)	8.67	17.34	5.00	8.67
Imidurea	0	0	0.3	0
Methylparaben	0.23	0.18	0	0.20
Propylparaben	0.06	0.06	0	0.05
Propylene glycol	11.56	7.50	0	15.00
Carboxy vinyl polymer	1.45	2.0	1.0	1.45
Potassium Hydroxide, 10% Aqueous Solution (QS)	pH 4.5	pH 4.3	pH 4.7	0
Trolamine, NF (QS)	0	0	0	6.5
Purified Water (QS ad)	100.00	100.00	100.00	100.00

The imidurea, methylparaben, propylparaben and/or propylene glycol were first dissolved in an amount of water equivalent to about 65 percent of the total batch amount. The carboxy vinyl polymer was then added slowly while the dispersion was vigorously mixed. While mixing, the potassium hydroxide solution or trolamine was added incrementally to the carboxyl vinyl polymer dispersion to achieve the desired pH. The benzoyl peroxide was levigated with a portion of the carboxy vinyl polymer dispersion and passed through a homogenizer or mill several times until the average particle size was less than 25 microns in diameter. Finally, the benzoyl peroxide dispersion and the remainder of the water were added and mixed into the suspension until homogeneous.

Example 9

Another aqueous suspension of benzoyl peroxide was prepared from pre-micronized benzoyl peroxide as follows:

Component	Weight Percent
Hydrous Benzoyl Peroxide, 40%, micronized	15.17
Propylene Glycol	11.5
Methylparaben	0.20
Propylparaben	0.05
Carboxy Vinyl Polymer	1.45
Potassium hydroxide, 10% Aqueous Solution (QS)	pH 4.5
Purified Water (QS ad)	100.00

The methylparaben, propylparaben and propylene glycol were dissolved in an amount of water equivalent to about 60 percent of the total batch amount. The carboxy vinyl polymer was then added slowly while the dispersion was vigorously mixed. While mixing, the potassium hydroxide solution was added incrementally to the carboxy vinyl polymer dispersion to achieve the desired pH. The benzoyl peroxide was mixed vigorously with the remaining portion of the water. Finally, the benzoyl peroxide slurry was added to the carboxy vinyl polymer dispersion and mixed until homogeneous.

Example 10

A kit was prepared which included (a) 4g of the clindamycin aqueous solution of Example 1 in a 4mL amber glass screw cap vial, (b) 26g of the benzoyl peroxide aqueous suspension from Example 5 in a 1 ounce wide mouth plastic jar, and (c) a disposable mixing spatula.

The components of the kit were admixed as follows:

1. The entire contents of the vial of clindamycin solution was added to the jar containing the benzoyl peroxide suspension; and
2. Using the disposable plastic spatula, the combination was mixed until the gel became homogeneous (about 1 minute).

An aesthetically pleasing white gel was produced containing about 5.26% benzoyl peroxide and about 1.2% clindamycin (1.4% measured as phosphate).

Example 11

A kit was prepared which included (a) 12g of the clindamycin aqueous solution of Example 1 in a 15 mL amber glass screw cap vial, (b) 78g of the benzoyl peroxide aqueous suspension from Example 6 in a 4 ounce wide mouth plastic jar, and (c) a disposable mixing spatula.

The components were admixed as follows:

1. The entire contents of the vial of clindamycin solution was added to the jar containing the benzoyl peroxide suspension; and

2. Using the disposable plastic spatula, the combination was mixed until the gel became homogeneous (about 1 minute).

An aesthetically pleasing white gel was produced containing about 10.5% benzoyl peroxide and about 1.2% clindamycin (1.4% measured as phosphate).

Example 12

A kit was prepared which included (a) 7.5g of the clindamycin aqueous solution of Example 2 in an 8mL amber glass screw cap vial, (b) 7.5g of the benzoyl peroxide aqueous suspension from Example 6 in a one-half ounce wide mouth plastic jar, and (c) a disposable mixing spatula.

The components were admixed as follows:

1. The entire contents of the vial of clindamycin solution was added to the jar containing the benzoyl peroxide suspension; and
2. Using the disposable plastic spatula, the combination was mixed until the gel became homogeneous (about 1 minute).

An aesthetically pleasing white gel was produced containing about 6.07% benzoyl peroxide and about 1.0% clindamycin (1.18% measured as phosphate).

Example 13

A kit was prepared which included (a) 8g of the clindamycin aqueous solution of Example 1 in an 8mL amber glass screw cap vial, (b) 22g of the benzoyl peroxide aqueous suspension from Example 7 in a one ounce wide mouth plastic jar, and (c) a disposable mixing spatula.

The components were admixed as follows:

1. The entire contents of the vial of clindamycin solution was added to the jar containing the benzoyl peroxide suspension; and
2. Using the disposable plastic spatula, the combination was mixed until the gel became homogeneous (about 1 minute).

An aesthetically pleasing white gel was produced containing about 2.56% benzoyl peroxide and about 2.3% clindamycin (2.8% measured as phosphate).

Example 14

Aqueous solutions of clindamycin phosphate were tested for chemical and physical stability at various pHs. Table 4 summarizes the clindamycin potency over time at various pH when stored at 40°C. Table 5 summarizes the physical stability over time at various pH when stored at room temperature.

Table 4

Sample No.	pH	Initial	1 Mo.	2 Mo.	3 Mo.
1	4.95	9.75	9.91	--	9.19
2	5.93	11.29	11.40	11.12	--
3	6.01	8.54	--	--	7.83
4	6.29	8.81	--	--	7.88

Table 5

Sample No.	pH	Initial	1 Mo.	2 Mo.	3 Mo.
1	4.95	clear soln	Heavy ppt.	Heavy ppt.	Heavy ppt.
2	5.69	clear soln	ppt.	ppt.	ppt.
3	5.93	clear soln	clear	clear	clear
4	6.01	clear soln	clear	clear	clear
5	6.20	clear soln	clear	clear	clear
6	6.29	clear soln	clear	clear	clear

Example 15

The stability of benzoyl peroxide suspension was studied for chemical and physical stability at various pH conditions at 40°C. Table 6 shows the physical stability as well as the assay results for benzoyl peroxide.

Table 6

pH	Test	Initial	1 Mo.	2 Mo.	3 Mo.
6.23	Benzoyl Peroxide Assay (%)	6.36	--	6.42	6.06
	Physical Stability	Homogeneous white gel	No change	No change	No change
5.80	Benzoyl Peroxide Assay (%)	8.19	8.19	8.39	8.16
	Physical Stability	Homogeneous white gel	No change	No change	No change
4.31	Benzoyl Peroxide Assay (%)	6.04	6.22	6.02	5.89
	Physical Stability	Homogeneous white gel	No change	No change	No change
4.22	Benzoyl Peroxide Assay (%)	5.91	5.96	---	---
	Physical Stability	Homogeneous white gel	No change	No change	No change

Example 16

The chemical stability of the composition containing both clindamycin and benzoyl peroxide, as the kit components are admixed by a pharmacist at the time of dispensing, was studied in an accelerated aging protocol. The effect of pH on stability of clindamycin in the presence of benzoyl peroxide is shown in Table 7 and Fig. 2.

Table 7

Loss after 1 month

Sample	pH	of aging at 40°C
1	6.96	43.3
2	6.55	35.3
3	5.99	25.5
4	5.71	30.0%
5	5.66	33.3%
6	5.57	27.9%
7	5.54	24.0%
8	5.49	24.7%
9	5.32	21.6%
10	5.08	22.3%
11	4.97	20.7%
12	4.85	20.5%
13	4.47	14.9
14	4.25	17.3
15	4.03	15.9

Example 17

Both clindamycin and benzoyl peroxide in the admixed gel from Example 10 were found to have a shelf-life of be several months at room temperature, as illustrated in Table 8.

Table 8

	Initial	1 Mo.	2 Mo.	3 Mo.
Clindamycin	1.20%	--	1.08%	1.01%
Benzoyl Peroxide	5.87%	--	5.83%	5.97%
Physical Appearance	Pleasant smelling, homogeneous white gel	No change	No change	No change

Example 18

Five patients with moderate acne vulgaris were treated with the topical gel of Example 10 for six weeks. Each patient applied the gel to his or her face twice daily. Results were evaluated by a dermatologist at weeks 2, 4, and 6, following a baseline pre-treatment evaluation.

In each patient, there was a marked reduction in the number of acne lesions during therapy as set forth in Table 9.

Table 9

Age (years)	20	16	17	18	22
Gender	female	female	male	female	female
Number of Inflammatory Lesions Before Treatment	29	14	14	12	14
After Treatment	6	8	7	7	0
Number of Non-Inflammatory Lesions Before Treatment	26	126	28	41	8
After Treatment	12	102	14	36	3
Dermatologist Assessment	E	G	VG	G	E

E = Excellent

VG = Very Good

G = Good

The dermatologist concluded that the topical gel was highly efficacious in reducing the number of inflammatory and non-inflammatory acne lesions. The dermatologist further concluded that the cosmetic elegance of the topical gel of the present invention (compared to the acne preparations previously used by the patients) likely contributed to the apparent high level of patient compliance in following the twice-a-day protocol regimen, thus contributing to the observed high efficacy. Each of the five patients rated the cosmetic elegance of the topical gel of the present invention as being "excellent" or "good," and every one rated its cosmetic elegance "better" than that of his or her previous or usual topical acne therapy.

Example 19

The material from Example 10 was compared to commercially available Benzamycin® (the commercial product corresponding to U.S. Patent No. 4,497,794), each product

having been admixed according to directions. Pharmaceutical appearance and physical properties were assessed. The composition of the present invention was found to be superior to Benzamycin® in pharmaceutical elegance, as shown below in Table 10.

Table 10

Quality	Topical Gel of Example 10	Benzamycin® Lot # 89449
Appearance	Soft, shiny white gel	dull, rubbery white gel
Homogeneity	uniform	grainy/syneresis

Example 20

An experiment was performed to determine the time required by the dispensing pharmacist to compound (admix) the kit in Example 10. For comparison, the same individual compounded Benzamycin® according to the manufacturer's instructions. The invention of the present application provided a significant saving of time for the pharmacist. The results are set forth in Table 11.

Table 11

	Kit of Example 10	Benzamycin Lot # 89449
Time to prepare liquid component	0 sec	1 min, 15 sec
Time to mix components completely (visual end point)	32 sec	1 min, 20 sec
Total time for pharmacist compounding	32 sec	2 min, 35 sec

Example 21

Thirteen human volunteers participated in a single-blind simultaneous bilateral symmetrical paired comparison of the topical gel of Example 10 and Benzamycin®. The gel from Example 10 was applied to one side of the face in a conventional manner. Benzamycin® was applied to the other side of the face in the same manner. A questionnaire was given to

the patients to assess the results. The topical gel of the present invention was highly preferred in each of the properties set forth in Table 12, and therefore represents a distinct improvement over Benzamycin®. Comments made by the volunteers further demonstrate the advantages and improvements. See Table 13.

Table 12

	Composition Preferred (No. of subjects)		
Cosmetic Property	Topical Gel of Example 10	Benzamycin Lot # 89449	No Preference
Spreadability	13	0	0
Feel/texture during application	13	0	0
Rub-in properties	13	0	0
Odor	8	4	1
Skin feel after application	10	1	2
Overall preference	13	0	0

Table 13

Descriptive evaluation of cosmetic properties:

	Typical volunteer comments
Benzamycin Lot # 89449	cold, chunky, difficult to spread, sticky, tendency to "ball-up," left residue, and dries slowly.
Example 10	aesthetically pleasant to use, easily spread, rubs in quickly, dries quickly, and is totally absorbed by skin.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A topical therapeutic composition comprising:

a pharmaceutically acceptable fluid carrier having a pH less than 7;

benzoyl peroxide present in the fluid carrier at from 1% by weight to 20% by weight; and

a clindamycin salt or ester present in the fluid carrier at from 0.2% by weight to 4% by weight.

2. A topical therapeutic composition as in claim 1, further comprising a gelling agent having enhanced viscosity at a pH below 7.

3. A topical composition as in claim 2, wherein the gelling agent is a carboxylated polymer.

4. A topical composition as in claim 1, wherein the gelling agent is polycarboxylmethylene present in the pharmaceutically acceptable fluid carrier at from 0.1% to 5% by weight, wherein the composition has a pH in the range from 4.5 to 5.5 and a viscosity in the range from $7x10^4$ cp to $12x10^4$ cp.

5. A kit for preparing a topical therapeutic composition, said kit comprising:

a first container holding a suspension of benzoyl peroxide in an aqueous gelling agent at a pH in the range from about 3.5 to 7.0;

a second container holding an aqueous solution of a clindamycin salt or ester at a pH in the range from 3.5 to 7; and

instructions to combine the benzoyl peroxide suspension with the clindamycin solution, whereby a stable product having a pH below 7 and an enhanced viscosity is obtained.

6. A kit as in claim 5, wherein the gelling agent is a carboxylated polymer.

7. A kit as in claim 6, wherein the carboxylated polymer is carboxy vinyl polymer and the pH of the suspension is in the range from about 4.0 to 5.0.

8. A kit as in claim 5, wherein the amounts of benzoyl peroxide suspension in the first container and the amount of clindamycin salt or ester solution in the second container are selected to provide a pH in the range from 4.5 to 5.5 and an increased viscosity when the total contents of each container are combined.

9. A kit for preparing a topical therapeutic composition, said kit comprising:

a first container holding a gelled aqueous suspension of benzoyl peroxide at a concentration from about 1% to 20% by weight, wherein the gel has a pH in the range from about 3.5 to 7.0 and a viscosity less than about $9x10^4$ cp at the pH;

a second container holding an aqueous solution of a clindamycin salt or ester at a concentration from 2% to 15% by weight and a pH from about 3.5 to 7; and

instructions to combine the benzoyl peroxide gelled suspension with the clindamycin solution at a weight ratio selected to provide a stable product having a pH below 7 and an enhanced viscosity.

10. A kit as in claim 9, wherein the gelled aqueous suspension in the first container includes a carboxylated gelling agent in an amount sufficient to provide a viscosity in the range from $5x10^4$ cp to $9x10^4$ cp at the pH of the suspension.

11. A kit as in claim 10, wherein the carboxylated gelling agent is carboxy vinyl polymer and the pH of the suspension is in the range from about 4.0 to 5.0.

12. A kit as in claim 11, wherein the pH of the clindamycin solution is in the range from about 6.0 to 6.5, and the relative amounts of the benzoyl peroxide suspension and the

clindamycin solution are such that the pH of the combination is in the range from 4.5 to 5.5.

13. A kit as in claim 12, wherein the amount of benzoyl peroxide suspension is from 2.5 g to 100 g and the amount of clindamycin solution is from 0.5 g to 60 g.

14. A method for preparing a topical therapeutic composition, said method comprising:

combining (a) a gelled aqueous suspension of benzoyl peroxide initially at a pH of 3.5 to 7.0 with (b) an amount of an aqueous solution of a clindamycin salt or ester at a pH of 3.5 to 7 selected to provide a pH of the combination below 7, whereby the product is stable and the viscosity of the product is greater than that of either the suspension or the solution.

15. A method as in claim 14, wherein the gelled aqueous suspension includes benzoyl peroxide at a concentration in the range from about 1% to 20%, a base present in an amount sufficient to adjust the pH to 4.0 to 5.0, and a gelling agent which provides a viscosity in the range from $5x10^4$ cp to $9x10^4$ cp at the pH.

16. A method as in claim 15, wherein the gelling agent is a carboxylated polymer.

17. A method as in claim 16, wherein the carboxylated polymer is carboxy vinyl polymer.

18. A method as in claim 17, wherein the aqueous solution of clindamycin has a pH in the range from 6.0 to 6.5 and is combined with the aqueous suspension in an amount to provide a pH of the combination in the range from 4.5 to 5.5 and a viscosity in the range from $7x10^4$ cp to $12x10^4$ cp.

19. A method as in claim 18, wherein the amount of benzoyl peroxide suspension is from 2.5 g to 100 g and the amount of clindamycin solution is from 0.5 g to 60 g.

20. A method for treating acne, said method comprising applying to affected skin areas a therapeutically effective amount of a composition comprising:

a pharmaceutically acceptable fluid carrier having a pH less than 7;

benzoyl peroxide present in the fluid carrier at from 1% by weight to 20% by weight; and

a clindamycin salt or ester present in the fluid carrier at from 0.2% by weight to 4% by weight.

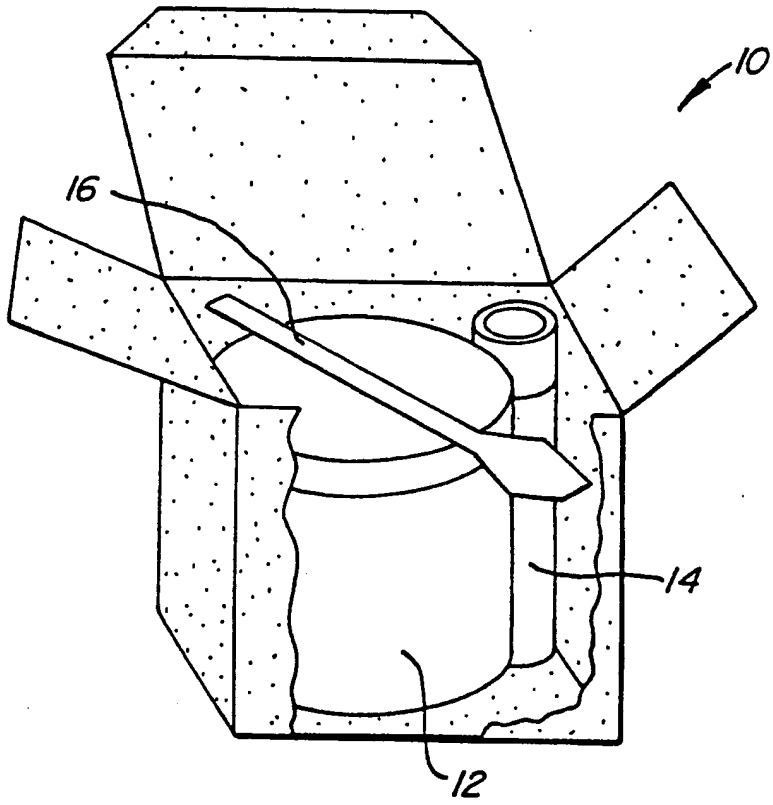

FIG. 1.

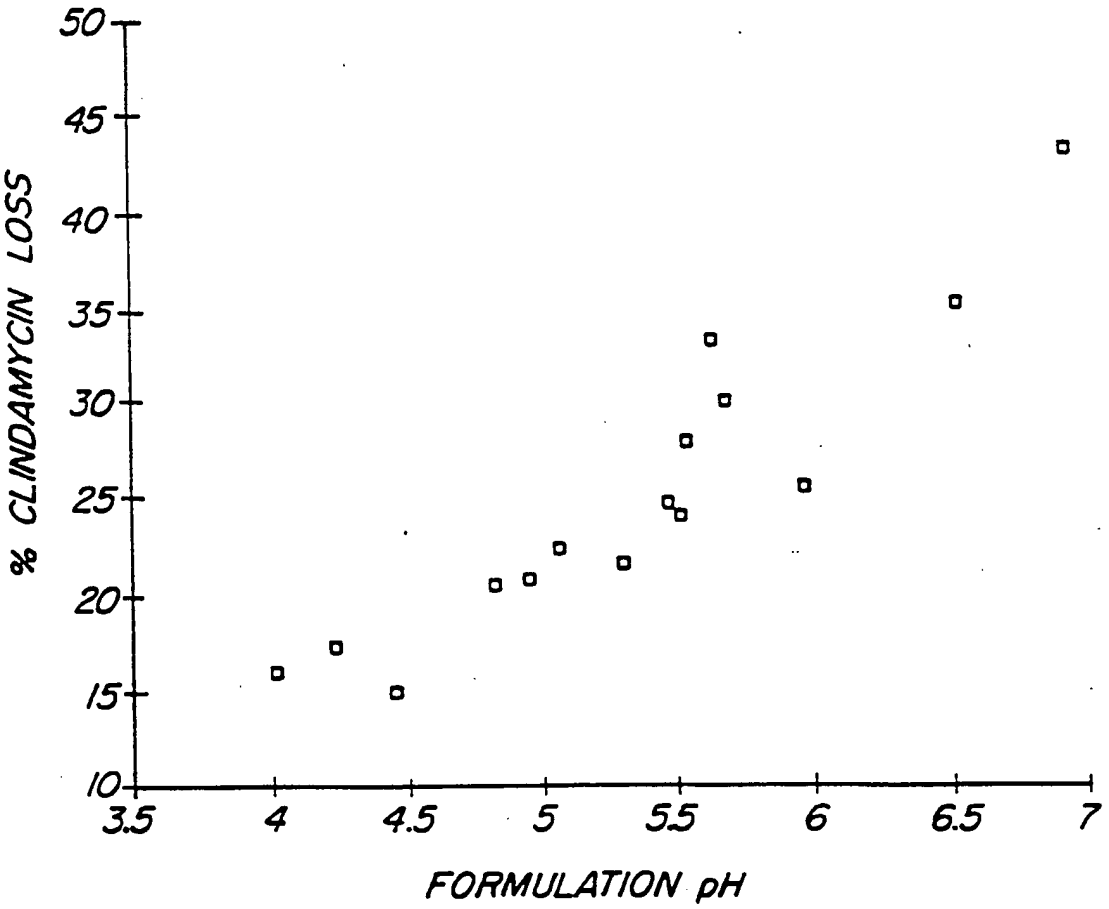
50
45
40
35
30
25
20
15
10
% CLINDAMYCIN LOSS
3.5
4
4.5
5
5.5
6
6.5
7
FORMULATION pH

FIG. 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/00464

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/12, 31/70
US CL :514/24, 679, 859
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/24, 679, 859

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,497,794 (Klein et al) 05 February 1985, col. 6, lines 5-50.	1-20
X	US, A, 4,505,896 (Bernstein) 19 March 1985, col. 6, lines 1-10.	1-20
Y	US, A, 4,731,362 (Hamashima et al) 15 March 1988, col. 4, lines 55-68.	2-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 APRIL 1993	09 APR 1993

Name and mailing address of the ISA/US	Authorized officer
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